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| 10/592,918 | 02/02/2007 | Toshihiro Nakajima | L7350.0011 | 2823 |

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| EXAMINER |
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SHIN, DANA H

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| ART UNIT | PAPER NUMBER |
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1635

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01/30/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/592,918

Applicant(s)

NAKAJIMA ET AL.

Examiner

Dana Shin

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-18 and 21-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-18 and 21-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 11-1-06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Currently, claims 1-6, 8-18, and 21-25 are pending and under examination on the merits.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 1, 2006 is being considered by the examiner. However, the JP or WO documents that are in non-English language are considered only insofar as their English abstracts.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8-15, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered

Art Unit: 1635

include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

The claims are drawn to pharmaceutical compositions and methods comprising the compositions wherein the compositions comprise an inhibitory substance for Synoviolin or hsHRD3. The term “substance” claimed in the instant application embraces any material of any origin as long as that material inhibits Synoviolin or hsHRD3. With regard to the term “substance”, the instant specification teaches that the “substance” is “preferably a siRNA (small interfering RNA) or shRNA (short hairpin RNA) against the gene encoding hsHRD3”. See page 3, lines 1-2 of the specification. The preferred embodiment of siRNA or shRNA molecule within the genus of “substances” is not a representative number of species sufficient to describe the claimed genus. Note that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure “indicates that the patentee has invented species sufficient to constitute the gen[us].” See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)(“[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.”). See also MPEP §2163.

Art Unit: 1635

In light of the above, the instant specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented the genus claimed in the instant case. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*.” (see page 1117).

Claims 1-6, 8-18, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting hsHRD3 expression in synovial cells *in vitro*, does not reasonably provide enablement for pharmaceutical compositions comprising siRNA or methods of treating diseases or inhibiting hsHRD3 expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in *Wands* states: “Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'.” (*Wands*, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of

Art Unit: 1635

one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1-6, 13-18, and 21-25 embrace only *in vivo* treatment methods for various diseases (e.g., RA, fibrosis, arthritis, cancers, osteoporosis, and cerebral neural diseases) and pharmaceutical compositions for *in vivo* use. The breadth of claims 8-12 embraces both *in vitro* and *in vivo* methods comprising inhibiting hsHRD3 expression and proliferation of synovial cells.

All claims in the instant case comprise a “substance” that inhibits HRD3, wherein the instant specification teaches that the “substance” is “preferably a siRNA (small interfering RNA) or shRNA (short hairpin RNA) against the gene encoding hsHRD3”. See page 3, lines 1-2 of the specification. As such, the instant claims are drawn to *in vivo* methods and pharmaceutical compositions comprising an RNAi agent that mediates RNAi.

The state of the art pertaining to RNAi-mediated therapeutics or *in vivo* use of RNAi agents as of the earliest filing date sought in the instant application was considered nascent. Even today, there is not a single siRNA (or shRNA) pharmaceutical agent recognized in the art, and neither is there a single guideline for *in vivo* use of siRNA or shRNA agents. Even more, the unpredictability of *in vivo* inhibitory activity of siRNA molecules remained unresolved as of February 7, 2007 as evidenced by the post-dated reference by Schmidt (*Nature Biotechnology*, March 2007, 25:273-275). As Schmidt discusses several RNAi patents, he points out that “Though RNAi has become invaluable for basic research, its therapeutic potential is unknown. Delivering RNAi drugs to target cells poses difficult challenges; largely because of this, drug-

Art Unit: 1635

development with RNAi remains mainly in preclinical stages.” See page 273.

Problems with *in vivo* administration of siRNAs still remain unresolved even today. In the article, Schmidt teaches that “It can be notoriously difficult for oligonucleotides to penetrate cell membranes, and evade immune system attacks. Without solving the delivery problem, drug makers will be unable to deliver on RNAi’s therapeutic promise.” See page 275. As evidenced by the post-dated reference by Schmidt, delivering siRNAs into the appropriate target cell or tissue still remains problematic in the art, and therefore the therapeutic potential of siRNAs would have been far from being well-known at the time of the invention.

The instant specification does not provide specific, useful teachings that are commensurate in scope with the claimed invention. The siRNA transfection methods exemplified in the instant specification do not bear a reasonable correlation to the entire scope of the claimed methods. For example, there is no adequate description of therapeutic efficacy of the claimed pharmaceutical compositions, and the exemplified *in vitro* data do not demonstrate any reasonable basis for one of ordinary skill in the art to practice the entire scope of the claimed methods, which embrace clinical, therapeutic applications of a relatively nascent technological innovation, namely RNAi-mediated gene therapy. Further, the *in vitro* inhibition of interleukin-6 production in synovial cells do not whatsoever demonstrate that an siRNA/shRNA construct targeted to hsHRD3 will treat myriad diseases such as the claimed RA, fibrosis, arthritis, cancers, osteoporosis, and cerebral neural diseases. Applicant’s attention is directed to *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) which teaches, “Nascent technology, however, must be enabled with a “*specific and useful teaching*” (original emphasis). The law requires an enabling disclosure for nascent technology because a person of

Art Unit: 1635

ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (emphasis added)

In view of the totality of the factors and reasons stated above, it is concluded that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims without undue experimentation. Hence, the claims are enabled only insofar as the *in vitro* methods of inhibiting HRD3 expression in synovial cells comprising transfecting an siRNA molecule targeted to SEQ ID NO:1 .

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step pertains to the step that achieves inhibition of hsHRD3 expression in synovial cells such as "comprising administering or introducing composition X into the synovial cells".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

Art Unit: 1635

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Rine et al. (US 6,107,462).

The claims are drawn to a pharmaceutical composition containing a substance that inhibits synovial cell proliferation, wherein the substance inhibits expression of human HRD3 and interleukin-6 production.

Rine et al. teach pharmaceutical compositions comprising polypeptides or nucleic acids that inhibit human HRD3 expression, which can be used to reduce hypercholesterolaemia. See columns 4, 13-14, 35-38, and 51. Although Rine et al. are silent about inhibiting interleukin-6 production by pharmaceutical compositions comprising polypeptides or nucleic acids that inhibit human HRD3 expression as claimed in claim 13, since the pharmaceutical compositions of Rine et al. meet the structural and functional limitations set forth in claims 14-15 and 17, it is reasonably concluded that the pharmaceutical compositions of Rine et al. would inherently inhibit interleukin-6 production, absent evidence to the contrary. Accordingly, all of claim limitations are taught by Rine et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

Art Unit: 1635

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 13-14, and 21-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/568,823. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the reference claims are drawn to pharmaceutical/therapeutic agents as well as methods that inhibit Synoviolin.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner